REMARKS/ARGUMENTS

Pending Claims and Amendments Thereto

Claims 1-12 and 21-23 are pending in this application. Claims 13-20 have been canceled as directed to a non-elected invention in response to an earlier restriction requirement. Claim 6 is indicated as withdrawn as directed to a non-elected species in response to a species election requirement; however, claim 6 is dependent on claim 1, which is under consideration. Claims 21 and 22 also are indicated as withdrawn. Claims 21 and 22 are directed to a non-elected invention in response to the earlier restriction requirement; however, claims 21 and 22 are method claims that involve the use of the product of elected (and currently being examined) claim 1. Accordingly, and consistent with standard restriction practice, Applicants respectfully request the rejoinder and examination of withdrawn claims 6, 21, and 22 upon an indication of the allowability of claim 1.

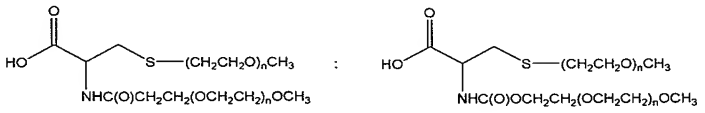
Applicants have amended claims 1, 9, 21, and 22 to correct grammar and improve readability. These claim amendments do not affect the scope of these claims. New claims 24-30 have been added and parallel claim 23 except for being dependent on claims 2-7 and 9, respectively. No new matter has been introduced by way of these claim amendments.

Priority

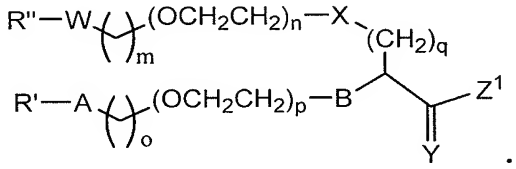
Claims 3-5 are denied the benefit of several provisional applications to which the present application claims priority (i.e., U.S. Provisional Patent Applications 60/527,082, 60/539,387, and 60/592,744) on the basis that the provisional applications allegedly fail to sufficiently disclose the subject matter of these claims. The Office Action states that the effective filing date for these claims is September 29, 2004, the filing date of U.S. Provisional Application 60/614,518. Applicants respectfully traverse.

Benefit of U.S. Provisional Patent Applications 60/592,744, filed July 29, 2004 is denied on the basis that this application allegedly does not "disclose the genus of branched polymers as recited in instant claims 3-5." The Office Action further alleges that "the prior filed application does not disclose varying the carbon chain length, designated as variable "q" in the instant claims." (Office Action, page 6). Applicants submit that the '744 provisional application does disclose branched polymers having a serine, cysteine, or di-lysine core as

described at paragraph 0117 of the '744 provisional application. The exemplary structures are provided in a simplified text format, without chemical figures. For example, a cysteine core branched PEG is identified as PEG-S-Cys-NHC(O)-OPEG rather than as:



, although both structures would be understood from the text version, in view of the skeletal structure provided at paragraph 0016:



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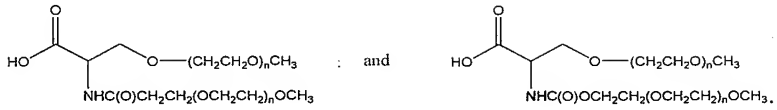
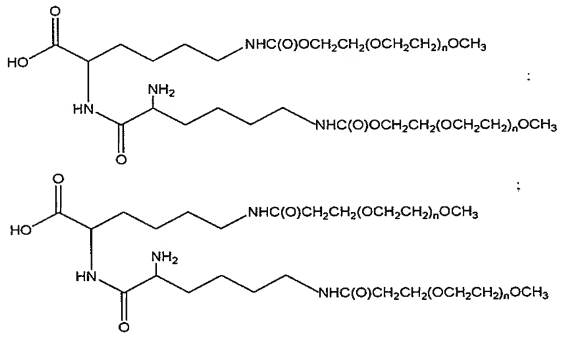
As the Office Action notes, the '744 provisional application contains a minor error in that variables A and B are not separately defined along with the other variables present in the provided skeletal PEG structures. However, one of ordinary skill in the art would immediately realize that variables A and B were intended to be included in the listing of symbols X, Y^1, Y^2, W, and U, as provided in paragraph 0114, since A and B are clearly analogous in position to variables X and W which are similarly defined. Based on this definition, variable B of the skeletal structure of paragraph 0016 would be selected from the group consisting of O, S, and N-R^4. R^4 is selected from the group consisting of "H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycloalkyl and substituted or unsubstituted heteroaryl." Therefore, N-R^4 would be understood by one of ordinary skill in the art to be NHC(O) or NHC(O)O, as, for example, shown in the cysteine core structures depicted above. As further evidence, the simplified text format of the cysteine core branched PEG actually specifies "... NHC(O)-OPEG" as an indication that an amide moiety is present at that position. Similar analyses apply to the serine core branched PEG structures, in which PEG-O-Ser-NHC(O)-OPEG is merely a simplified text version representative of



Likewise, (PEGO-C(O)NH)$_2$Lys-Lys-NHC(O)-OPEG is merely a simplified text version representative of structures such as:



Although the currently claimed species are fully disclosed in the '744, '518, and '387 provisional applications, Applicants respectfully reiterate that U.S. Provisional Application 60/527,082 is adequate to support a priority date of December 3, 2003. One of ordinary skill in the art would have been able, as of December 3, 2003, to make and use the PEG conjugates of claims 3-5 using the disclosure of the '082 provisional application in view of the state of the art at the time. Numerous references are identified in the '082 provisional application, which references teach PEG derivatives contemplated for use in the invention disclosed therein (see, e.g., page 31, line 9, through page 32, line 16, of the '082 provisional application as well as paragraphs 0105-0113 of the '744 provisional application). U.S. Patent Application Publication 2007/0032405, filed July 31, 2006, cites additional references relating to branched PEG moieties:

> Branched polymers based upon poly(ethylene glycol) are known in the art. For example, Greenwald et al. (WO93/41562) discloses a branched PEG that is based on a 1,3-diamino-2-propanol core. Morpurgo and co-workers discuss the use of branched PEG based on a lysine core is discussed [sic] in *Appl. Biochem. Biotechnol.* 56:59-72 (1996). A similar lysine-based branched PEG was prepared by Cuiotto et al., *Bioorg. Med. Chem. Lett.* 12:177-180 (2002). Harris et al. (U.S. Patent No. 5,932,462) also prepared a branched PEG that is based upon lysine. Martinez et al. (U.S. Patent No. 5,643,575) describe a number of branched PEG species that are based upon various core structures and the conjugation of

> these species with a biologically active material (U.S. Patent No. 6,113,906).

(paragraph 0013). In considering references such as these in combination with the disclosure of the '082 provisional application, but certainly in combination with the disclosure of the '744 provisional application, one of ordinary skill in the art would have been able to make and use PEG conjugates such as those of claims 3-5, and would have understood that the inventors of the '082 provisional application were in possession of PEG conjugates such as those of claims 3-5.

Information Disclosure Statement

In response to the Examiner's indication in the Office Action that a copy of the Kawasaki reference was not included with the previously submitted Information Disclosure Statement, Applicants note that the Kawasaki reference was originally cited on the PTO-892 document accompanying the Office Action mailed December 17, 2009. Applicants mistakenly added the document to the Information Disclosure Statement filed April 20, 2010. Applicants therefore believe no further copy of Kawasaki is required.

Discussion of Rejection Under 35 U.S.C. § 102(e)

Claims 1, 2, 7-12 and 23 are rejected as anticipated by International Patent Application Publication WO 03/031464 (the "DeFrees PCT Publication") as evidenced by Ulloa-Aguirre et al., *Endocrine, 11(3)*: 205-215 (1999), and U.S. Patent Application Publication 2003/0166525 (Hoffman et al.). As noted by the Office Action, the DeFrees PCT Publication names as inventors three individuals, Shawn DeFrees, Robert J. Bayer, and Caryn Bowe, who were also named in the filing papers for the present application.

Applicants note Robert Bayer was not properly named as an inventor with respect to the present application. Accordingly, pursuant to 37 C.F.R. § 1.48(a), documents are filed herewith removing Robert Bayer as a named inventor.

Applicants submit herewith Declarations Under 37 C.F.R. § 1.132 by co-inventors DeFrees and Bowe, stating that the cited portions of the presently claimed invention disclosed but not claimed in the DeFrees PCT Publication were invented by them or derived from them (i.e., DeFrees and/or Bowe). In view of the removal of Robert Bayer from the present application, Rule 132 declarations are submitted herewith for all named inventors of the

present application. Therefore, the DeFrees PCT Publication is not "by another" as required under 35 U.S.C. § 102(e), and the DeFrees PCT Publication is effectively removed as prior art against the present claims. Under the circumstances, Applicants respectfully request reconsideration and withdrawal of the anticipation rejection.

Discussion of Rejection Under 35 U.S.C. § 103

A. Office Action "Section [0004]"- Claims 3-5

Claims 3-5 are rejected under 35 U.S.C. § 103 as obvious over the DeFrees PCT Publication in view of Ulloa-Aguirre et al., *Endocrine, 11(3)*: 205-215 (1999), and U.S. Patent Application Publication 2003/0166525 (Hoffman et al.).

As noted above, Applicants submit herewith Declarations Under 37 C.F.R. § 1.132 by co-inventors DeFrees and Bowe, stating that the cited portions of the presently claimed invention disclosed but not claimed in the DeFrees PCT Publication were invented by them or derived from them (i.e., DeFrees and/or Bowe). Therefore, the DeFrees PCT Publication is not "by another" as required under 35 U.S.C. § 102(e). As such, the DeFrees PCT Publication cannot form a basis for rejection under 35 U.S.C. § 103.

The Office Action cites the DeFrees PCT Publication as teaching methods and compositions for remodeling a peptide molecule including the addition or deletion of one or more glycosyl groups to the peptide, and/or the addition of a modifying group to the peptide, such as poly(ethylene) glycol (Office Action, page 23-24). In rejecting claims 3-5 as obvious over the DeFrees PCT publication, the Office Action relies on Hoffman merely to provide a human FSH sequence (Office Action, page 25). The Office Action cites Ulloa-Aguirre as identifying glycosylation sites of FSH (Office Action, page 25). These other references fail to teach FSH peptide conjugates, much less the conjugates recited in claims 3-5, and therefore fail to support a prima facie case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

B. Office Action "Section [0001]" – Claims 1, 2, 7- 12, and 23

Claims 1, 2, 7- 12, and 23 are rejected as obvious over EP0605963 (Wright) in view of U.S. Patent Application Publication 2002/0016003 (Saxon), U.S. Patent 5,643,575 (Martinez), and Keene et al., *J. Biol. Chem.* 264(9): 4769-4775 (1989) as evidenced by U.S.

Patent 6,586,398 (Kinstler), Gervais, *Glycobiology, 13(3)*: 179-189 (2003), Ulloa-Aguirre et al., *Endocrine, 11(3)*: 205-215 (1999), and Kawasaki, *Analytical Biochem., 285*: 82-91 (2000).

The Office Action alleges that Wright teaches "methods and compounds for modifying polypeptides with PEG or other water-soluble organic polymers," and further that Wright teaches that it is advantageous "to couple water-soluble reagents to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids" (Office Action, page 9). The Office Action cites Kinstler as allegedly curing Wright's deficiency of failing to teach PEGylation of EPO using sodium periodate oxydation of EPO followed by conjugation of the resulting aldehyde with PEG (Office Action, page 11). The Office Action further characterizes the deficiency of Wright as a failure to "expressly teach conjugation of the PEG polymer to the 9-position or 5-position of sialic acid, as recited in the instant claims." Furthermore, the Office Action, admits that Wright does not teach the use of FSH in the disclosed methods (Office Action, page 11).

The Office Action alleges that Saxon teaches the incorporation of synthetic sialic acid azido-derivatives into the sialic acid biosynthetic pathway, eventually resulting in the incorporation and expression of the synthetic sugar residues on glycoproteins. The Office Action then alleges that the azido-modified glycoprotein can undergo a chemoselective ligation with a phosphine-bearing ligand which can allegedly result in an amide or thioamide bond, with release of nitrogen and an oxidized phosphine byproduct (Office Action, page 12). The Office Action cites Example 6 as depicting the incorporation of N-axidoacetylmannosamine into cell surface glycans "as detected by labeling of the cells with biotin modified with a phospine group," and Example 7 as depicting "a method wherein two peptides, one modified with an azido group, and the other modified with a phospine group, are conjugated together to form an amide bond between the two peptides" (Office Action, page 12). The Office Action further alleges that Saxon discloses that "previous work showed that incorporation of a ketone-bearing group, such as a levulinoyl group, can be expressed on glycoproteins as SiaLev, wherein the levulinoul group is present at the 5-position of sialic acid, and can be chemoselectively conjugated to compounds or other molecules bearing a hydrazide group" (Office Action, page 12-13).

The Office Action cites Martinez as teaching "branched, non-antigenic polymers and conjugation of the polymers to biologically active molecules such as proteins and peptides as a means to extend their circulating half-life" (Office Action, page 13).

Keene, Gervais, and Ulloa-Aguire are alleged to provide various properties of FSH as well as methods of cloning and expression FSH, which are not taught or suggested by Wright, Saxon, Martinez, or Kinstler.

As previously noted by Applicants, Wright, Martinez, Kinstler, Gervais, and Ulloa-Aguire do not teach or suggest an FSH peptide coupled to PEG via an "intact glycosyl linking group" as presently claimed. Keene further does not cure this deficiency, being directed generally to cloning and expression of rhFSH in CHO cells. Saxon also fails to teach or suggest a method for coupling PEG to FSH via an "intact glycosyl linking group" according to the structures provided, e.g., in claim 1.

The cell surface ketone reactions described and shown at paragraphs 0008-0010 of Saxon, which Saxon identifies as prior art, involve the application of N-levulinoylmannosamine ("ManLev") to living cells, which "permits the metabolism of the unnatural ManLev precursor into sialic acid analogs on living cells, resulting in the display of ketones ... on the cell surface" (Saxon at paragraph 0008). Saxon alleges that these displayed ketones can then be further modified "with any moiety bearing a hydrazide or aminooxy group" (Saxon at paragraph 0008). However, such a statement appears to overreach the actual disclosure of the reference cited therein (i.e., Mahal et al., *Science*, 276: 125 (1997), of record). In particular, Mahal recites only the linkage of biotinamido-caproyl hydrozide, a small biotin-based molecule (Mahal, page 1126). Although Mahal speculates that "[i]n principle, any hydrazide-derivatized molecule can be used to selectively remodel the surface of ketone-expressing cells" (Mahal, page 1126, Figure 1 legend), Saxon's own disclosure demonstrates that an azide coupling is not equally succesful for all reagents. One of ordinary skill in the art would not assume, based on Mahal's and Saxon's disclosures, that PEG would be successfully conjugated using the reactions and reagents provided therein.

At Figure 13 of Saxon, which is described in Example 7, an acetate-amide linkage is unsuccessfully attempted. Saxon notes that, while both anhydrous and aqueous conditions were studied, "only azide reduction to the amine was observed, without the desired acetate

transfer (Saxon at paragraph 0211). Saxon posits that the reaction might be successful if one were to "increase the rigidity of the linkage between the phospine and the ester, as in ... Scheme 18, for the desired reaction to take place" (Saxon at paragraph 0211). The reaction depicted in Scheme 18, however, appears to be merely prophetic with no evidence that it would be more successful than the failed reation of Figure 13 (and neither Scheme 18 nor Figure 13 depicts a linkage that would conform precisely to C_5 or C_9 of present claim 1). In fact, nearly all of the reactions which were allegedly successfully completed by Saxon include an aromatic linker. See, e.g., Example 6 and Example 8 of Saxon, with accompanying figures. The other ligation reaction recited by Saxon, a peptide-peptide linkage provided in Example 7, also represents a particular situation in which the connected moieties are designed for stability, and further includes aryl or cycloalkyl groups. Specifically, R_1 and R_2 as required in Scheme 14 are defined at paragraphs 0080 and 0081 of Saxon. R_1 is defined as "an electrophilic group to trap (e.g., stabilize) an aza-ylide group," while R_2 is defined as follows: "R_2 and R_3 are generally aryl groups, including substituted aryl groups, or cycloalkyl groups (e.g., cyclo-hexyl groups) where R_2 and R_3 may be the same or different, preferably the same."

Because Saxon relies upon the importance of a "rigid linkage" such as an aryl or additional cycloalkyl, in combination with an electrophilic "trap" to support the moieties being attached, one of ordinary skill in the art would not expect a relatively fluid molecule such as PEG to be suitable for conjugation using the methods disclosed therein. Similar to the Office Action's characterization of the deficiency of Wright, Saxon fails to "expressly teach conjugation of the PEG polymer to the 9-position or 5-position of sialic acid, as recited in the instant claims." Inasmuch as the cited references cannot be combined to provide an FSH peptide coupled to PEG via an "intact glycosyl linking group" as presently claimed, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

C. Office Action "Section [0002]" – Claims 3-5

Claims 3-5 are rejected as obvious over EP0605963 (Wright), in view of U.S. Patent Application Publication 2002/0016003 (Saxon), U.S. Patent 5,643,575 (Martinez), and Keene et al., *J. Biol. Chem.* 264(9): 4769-4775 (1989), as evidenced by U.S. Patent 6,586,398 (Kinstler), Gervais, *Glycobiology, 13(3)*: 179-189 (2003), Ulloa-Aguirre et al., *Endocrine*,

11(3): 205-215 (1999), and Kawasaki, *Analytical Biochem.*, *285*: 82-91 (2000), and further in view of Felix et al., *J. Peptide Research*, *63*: 85-90 (2004).

The Office Action applies Wright, Saxon, Kinstler, Martinez, Gervais, Ulloa-Aguirre, and Kawasaki as described above with respect to the rejections labeled "Section [0001]" in the Office Action and further applies Felix. The Office Action admits that Wright, Saxon, Kinstler, and Martinez do not teach the particular branched PEG structures recited in claims 3-5, but alleges that Felix cures the deficiency due to its recitation of lysine and glutamate "as linkers for generating branched polymers" (Office Action, page 22). As discussed above, Wright, Saxon, Kinstler, Martinez, Gervais, Ulloa-Aguirre, and Kawasaki do not recite an FSH peptide coupled to PEG via an "intact glycosyl linking group" as presently claimed. The Office Action does not allege that Felix addresses this feature, and indeed it does not. Therefore, the cited references do not teach or suggest every element of the rejected claims and fail to properly support the obviousness rejection.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Obviousness-type Double Patenting

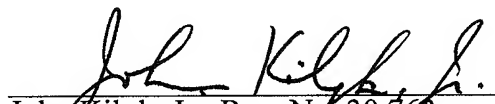
Claims 1, 7, 9, and 23 are rejected as obvious over U.S. Patents 7,473,680, 7,416,858, and 7,138,371. Applicants will file a terminal disclaimer over the '680, 858, and '371 patents upon a determination that one or more claims in the present application is otherwise allowable and remain subject to an obviousness-type double patenting rejection over the claims of the '680, 858, and '371 patents.

Claims 1, 3, 10, and 23 are provisionally rejected as obvious over U.S. Patent Applications 12/418,530, 12/152,587, 11/781,885, 11/781,900, 11/781,888, 11/866,969, 11/781,896, 11/781,902, and 11/714,874. U.S. Patent Applications 11/781,900, 11/781,896, 11/781,902, and 11/714,874 are abandoned, and therefore the rejections are rendered moot as to these applications. U.S. Patent Applications 12/152,587, 11/781,885, 11/781,888, and 11/866,969 are pending. In view of the provisional nature of the obviousness-type double patenting rejection as based on these pending patent applications, Applicants respectfully request that this portion of the obviousness-type double patenting rejection be held in abeyance until the present application otherwise is deemed allowable.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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